Synthesis of Nipagin Esters Using Acidic Functional Ionic Liquids as Catalysts

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GRAPHICAL ABSTRACT

$$\text{HO-C}_6\text{H}_4\text{-COOH} + ROH \xrightarrow[\triangle]{TSILs} \text{HO-C}_6\text{H}_4\text{-COOR} + H_2O$$

$$R = C_2H_5 ;\ C_4H_9 ;\ C_8H_{17} ;\ C_{12}H_{25}$$
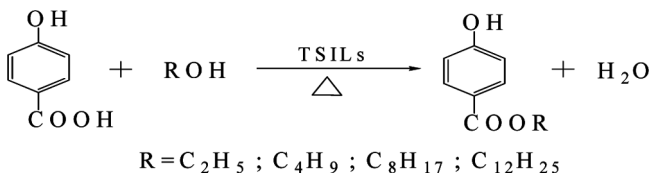
Abstract *Several Brønsted acidic functional ionic liquids (FILs) with an alkane sulfonic acid group were synthesized. These FILs as dual solvent-catalysts for Nipagin esterification reactions were investigated. The results indicated that [HSO₃-pMIM]HSO₄ has the best catalytic activity and recyclability among the various kinds of FILs investigated, and its structure was characterized by infrared and NMR. The [HSO₃-pMIM]HSO₄ could be easily separated from the reaction mixture and reused without noticeably decreasing the catalytic activity.*

Keywords Acidic functional ionic liquids; catalysis; Nipagin ester; synthesis

INTRODUCTION

Nipagin ester (also known as hydroxylbenzoate) has been considered a safe and effective preservative and antibacterial agent. At present, studies of high-carbon Nipagin esters have been focused on heptyl Nipagin and octyl Nipagin,[1,2] but these products have not been used in industry, and series of such products has not been researched.[3,4]

Nipagin esters were synthesized using sulfuric acid as catalyst in a homogeneous reaction system. The sulfuric acid cannot be reused and has other
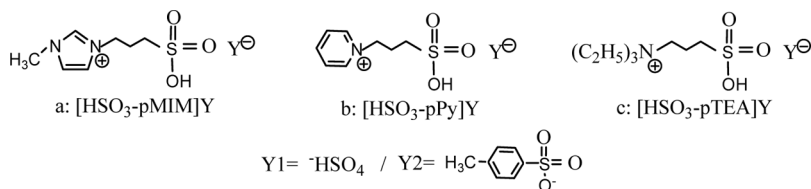
Figure 1. Structure of FILs.

disadvantages such as equipment corrosion, more by-products, tedious workup procedure, and environmental problems. Although the corrosion and pollution of organic acid[5,6] are less than that of sulfuric acid, wastes are still a big problem. Organic acid also cannot be recycled like sulfuric acid. Solid catalysts[7–10] are non-volatile materials, benign to the environment, and can be easily separated from the product, but they have some shortcomings such as high molecular weight/active-site ratios and rapid deactivation from coking, which limits their application.

Ionic liquids (ILs) have been considered as promising, environmentally benign alternatives.[11–15] Since Cole et al.[11] first reported Brønsted acidic FILs that bear an alkane sulfonic acid group in an imidazole and triphenylphosphine cation, more attention has been focused on these FILs.[16–21] Such Brønsted acidic FILs have shown very high activity and selectivity in many esterifications as dual solvent–catalysts.[22–25] Moreover, compared with the traditional catalyst, the FILs are also recyclable and are tunable to satisfy specific chemical tasks,[16,26,27] such as acid–base, solubility, stability, and so on.

In this article, several novel SO$_3$H-functional Brønsted acidic FILs (Fig. 1) that bear an alkane sulfonic acid group in N-methylimidazole, pyridine, and triethylmine cations are reported, and their catalytic activities for preparation of Nipagin esters are also investigated.

EXPERIMENTAL

Chemicals and Instruments

The infrared (IR) spectra were run on a Nicolet 510P Fourier transform (FT)–IR spectrometer and are expressed in centimeters^{-1} (KBr). ^{1}H NMR spectra were recorded on a Bruker AV500 (500 MHz, D$_2$O), and ^{13}C NMR spectra were measured on a Bruker AV500 (75.5 MHz, D$_2$O), spectrometer. Thermogravimetry (TG) was run on a STA-449C DSC-TG apparatus.

All chemicals (analytical-reagent grade) were commercially available and used without further purification.

Preparation of Acidic FILs

For this article, the general syntheses of acidic FILs involve a two-step process as described in the literature.[11,28,29] Taking 1-methyl-3-propanesulfonic-imidazolium hydrogensulfate [HSO$_3$-pMIM]HSO$_4$, for example, the zwitterionic-type
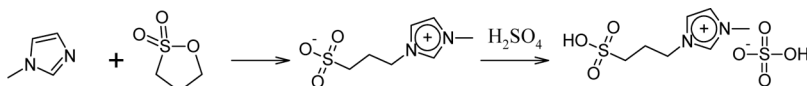
Scheme 1. Synthesis of FILs.

$$R = C_2H_5 \; ; \; C_4H_9 \; ; \; C_8H_{17} \; ; \; C_{12}H_{25}$$
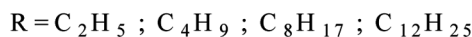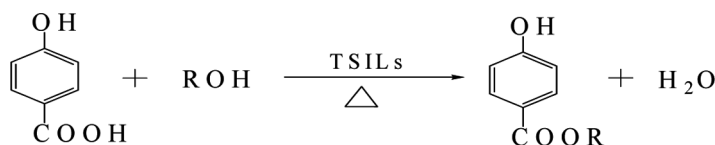
Scheme 2. Esterification in FILs.

precursors (MIM-PS) were prepared through a one-step direct sulfonation reaction (Scheme 1), then followed by a proton reaction using acid addition (Scheme 2).

In accordance with the same method, acidic FILs [HSO$_3$-pMIM]pTSA, [HSO$_3$-pPy]HSO$_4$, [HSO$_3$-pPy]pTSA, [HSO$_3$-pTEA]HSO$_4$, and [HSO$_3$-pTEA]pTSA were prepared, and they are all pale yellow viscous liquids at room temperature. The FILs were analyzed by NMR and IR, and the spectral data agreed with their structures.

Spectral data for MIM-PS. ^{1}H NMR (500 MHz, D$_2$O):δ 2.26 (m, 2H), 2.86 (t, 2H), 3.83 (s, 3H), 4.30 (t, 2H), 7.38 (s, 1H), 7.46 (s, 1H), 8.70 (s, 1H); ^{13}C NMR (125 MHz, D$_2$O):δ 24.79, 35.46, 46.97, 47.41, 121.85, 123.50, 135.82; IR (KBr, ν/cm^{-1}): ν 3450, 3154, 3110, 2962, 1640, 1575, 1461, 1424, 1195, 1043, 746, 622, 532.

Spectral data for [HSO$_3$-pMIM]HSO$_4$. ^{1}H NMR (500 MHz, D$_2$O): δ 2.11 (m, 2H), 2.71 (t, 2H), 3.71 (s, 3H), 4.16 (t, 2H), 7.25 (s, 1H), 7.32 (s, 1H), 8.53 (s, 1H); IR (KBr, ν/cm^{-1}): $\nu$ 3437, 3157, 2970, 1722, 1653, 1574, 1462, 1425, 1230, 1203, 1172, 1078, 1055, 1029, 880, 853, 748, 698, 655, 582, 528; DSC-TG (N$_2$, 10 °C/ min):single decomposition peak, Td 366.4 °C, weightlessness 81.57%.

Nipagin Esterification

p-Hydroxylzoic acid, alcohol, and FILs were added to a 50-mL flask with a thermometer, water segregator, and reflex condenser. Under vigorous stirring and heating, the esterification reaction was carried out for the desired time. Through crystallization, the produced esters can be gained (Scheme 2).

RESULTS AND DISCUSSION

Esterification with Acidic FILs

The esterifications of low-carbon alcohol Nipagin were carried out using the synthesized FILs, traditional acid, and solid catalyst as catalysts, respectively, and

Table 1. Synthesis of low-carbon Nipagin esters

ROH	Catalyst	Entry	n_{acid}:$n_{alcohol}$:n_{cat}	T (°C)	Time (h)	Yield (%)
C_2H_5OH	H_2SO_4	1	1:4.0:0.1	85–100	3	88.0
	p-CH$_3$–phSO$_3$H[5]	2	1:4	–	3.5	75.0
	JK008 resin[7]	3	1:5.5	72–110	6	91.7
	SO$_4^{2-}$/TiO$_2$[8]	4	1:4	115–135	4	93.2
	TiSiW$_{12}$O$_{40}$/TiO$_2$[9]	5	1:4	84–92	2	87.5
	[HSO$_3$-pMIM]HSO$_4$	6[a]	1:4.0:0.1	75	5	72.9
		7[a]	1:4.0:0.1	75	6	77.8
		8	1:4.0:0.1	85–100	3	91.3
		9	1:4.0:0.15	85–100	3	92.3
		10	1:3.0:0.15	85–100	3	93.7
		11[b]	1:3.0:0.15	85–100	3	95.8
	[HSO$_3$-pMIM]pTSA	12	1:4.0:0.1	85–100	3	90.5
	[HSO$_3$-pPy]HSO$_4$	13	1:4.0:0.1	85–100	3	83.4
	[HSO$_3$-pPy]pTSA	14	1:4.0:0.1	85–100	3	85.5
	[HSO$_3$-pTEA]HSO$_4$	15	1:4.0:0.1	85–100	3	87.5
	[HSO$_3$-pTEA]pTSA	16	1:4.0:0.1	85–100	3	87.6
C_4H_9OH	H_2SO_4	17	1:3.5:0.1	125–135	1	86.1
	NaHSO$_4$·H$_2$O[10]	18	1:2.0:0.072	130–170	5	92.8
	TiSiW$_{12}$O$_{40}$/TiO$_2$[9]	19	1:4	84–92	2	91.1
	[HSO$_3$-pMIM]HSO$_4$	20	1:3.5:0.1	125–135	1	87.1
		21	1:3.5:0.1	125–135	2	91.0
		22	1:3.5:0.1	125–135	3	92.7
		23[b]	1:3.5:0.1	125–135	3	95.3
	[HSO$_3$-pMIM]pTSA	24	1:3.5:0.1	125–135	1	86.8
	[HSO$_3$-pPy]HSO$_4$	25	1:3.5:0.1	125–35	1	86.4
	[HSO$_3$-pPy]pTSA	26	1:3.5:0.1	125–135	1	86.1
	[HSO$_3$-pTEA]HSO$_4$	27	1:3.5:0.1	125–135	1	84.3
	[HSO$_3$-pTEA]pTSA	28	1:3.5:0.1	125–135	1	84.8

[a]Benzene as water-segregated reagent.
[b]Double the amount of reactants.

the results are listed in Table 1. As seen from Table 1, in the synthesis of ethyl Nipagin (entries 1–16), the FILs showed better catalytic activity than a traditional acid and solid catalysts. On the one hand, using FILs as catalyst, the produced esters gained the same yields (about 85%) as using a traditional acid as catalyst (entries 1 and 2), and the color and purity of the produced esters are better than when using traditional acid as catalyst. On the other hand, the FILs reported here have a certain polarity and were dissolved in the reaction system so that esterification is homogeneous. Compared with the solid catalyst (entries 3–5), the FILs can increase reaction rate, shorten reaction time, and reduce energy consumption. With the same cation, the FILs with sulfuric anion and p-methyl benzenesulfonic anion revealed the same catalytic activity and received a similar ester yield. However, with the same anion, imidazole FILs (entries 8 and 12) gained the best ester yield (> 90%), the second is triethylamine FILs (entries 15 and 16), and the last is pyridine FILs (entries 13 and 14). This is because the catalytic activity of FILs is related to their Brønsted acidic strength and the stability in esterifications.[29] The pyridine ring and imidazole ring withdraw electrons, while the ethyl group donates an electron. Therefore, the

density of positive charge on the nitrogens of pyridine and imidazole is larger than on that of triethylamine. In comparison with pyridine FILs, the positive charge is dispersed for the imidazole because of the conjugative effect. The Brønsted acidic strengths of the FILs with different nitrogen groups are in the sequence pyridine > N-methylimidazole > triethylamine, and the stability of the FILs is triethylamine > N-methylimidazole > pyridine.[30] Similarly, in the synthesis of butyl Nipagin (entries 17–28), imidazole FILs (entries 20 and 24) also showed better catalytic properties and gained the same yield (87%) as sulfuric acid (entry 17) after 1 h. Compared with solid catalyst (entries 18 and 19), using FILs as catalyst, the esters were produced in higher yield and shorter reaction time. Finally, FIL [HSO_3-pMIM]HSO_4 was used as catalyst for synthesizing a series of Nipagin esters. The results of synthesizing high-carbon Nipagin esters are listed in Table 2. From Table 2 we can see that in the synthesis of high-carbon Nipagin esters, the imidazole FILs also showed the same predominances as in low-carbon Nipagin esters.

In addition, reaction temperature is one of the important factors for esterification. At too low of a temperature, the reaction rate was slow and the esters were produced in poor yield; at too high of a temperature, the esterification was prone to form ether and carbonation, which brings difficulties to the separation and purification. In the synthesis of ethyl Nipagin (Table 1, entries 1–16), according to the ethanol–water azeotropic principle, the ester yield markedly improved to 91.3% without any water-segregated reagent (Table 1, entry 8). Under the optimal reaction conditions (Table 1, entry 10), the yield reached 93.7%. In the synthesis of butyl Nipagin (Table 1, entries 17–28), the amount of n-butanol directly impacts the reaction temperature. Under the optimal reaction conditions (Table 1, entry 22), the yield was 92.7%. In the synthesis of octyl Nipagin (Table 2, entries 1–9), when the reaction temperature rose above 135 °C, crystallization went with the oil-like substance, while the yield was lower. Under the optimal reaction conditions (Table 2, entry 7), the yield was 94.6%. Similarly, the yield of dodecyl Nipagin was 94.8% when reacted for 4 h at 130–140 °C (Table 2, entry 14).

Table 2. Synthesis of high-carbon Nipagin esters

ROH	Catalyst	Entry	n_{acid}:$n_{alcohol}$:n_{cat}	T (°C)	Time (h)	Yield (%)
$C_8H_{17}OH$	H_2SO_4	1	1:3.0:0.1	120–135	3	89.8
	[HSO_3-pMIM]HSO_4	2	1:3.0:0.1	100–110	3	87.0
		3	1:3.0:0.1	110–120	3	92.4
		4	1:3.0:0.1	120–130	3	94.6
		5	1:3.0:0.1	130–140	3	87.6
		6	1:3.0:0.1	140–150	3	83.6
		7	1:3.0:0.1	120–135	3	94.6
		8[a]	1:3.0:0.1	120–135	3	97.1
	[HSO_3-pMIM]pTSA	9	1:3.0:0.1	120–135	3	93.8
	p-CH_3-phSO_3H [6]	10	1:3.0:0.07	130–140	4	90.1
$C_{12}H_{25}OH$	[HSO_3-pMIM]HSO_4	11	1:4.0:0.1	120–130	3	87.4
		12	1:4.0:0.1	130–140	3	93.6
		13	1:4.0:0.1	140–150	3	83.2
		14	1:4.0:0.1	130–140	4	94.8

[a]Double the amount of reactants.

Table 3. Effect of reusing [HSO$_3$-pMIM]HSO$_4$ on results of esterification

No.	1	2	3	4	5	6	7	8
Yield of ester 1[a] (%)	93.7	93.6	93.4	93.1	92.8	92.5	92.0	91.3
Recovery yield of ILs for synthesizing ester 1[a] (%)	97.9	96.8	94.7	91.6	89.5	87.4	84.2	80.0
Yield of ester 2[b] (%)	92.7	92.4	91.8	91.2	89.8	88.7	91.5	
Recovery yield of ILs for synthesizing ester 2[b] (%)	93.3	83.3	78.3	71.7	65.2	53.3		
Yield of ester 3[c] (%)	94.6	94.0	93.6	92.0	89.6			
Recovery yield of ILs for synthesizing ester 3[c] (%)	84.1	73.3	60.5	46.8				

[a]Ester 1 = ethyl Nipagin, the reaction condition: n_{acid}:$n_{alcohol}$:n_{cat} = 1:3.0:0.15, 85–100 °C, 3 h.
[b]Ester 2 = butyl Nipagin, the reaction condition: n_{acid}:$n_{alcohol}$:n_{cat} = 1:3.0:0.10, 125–135 °C, 3 h.
[c]Ester 3 = octyl Nipagin, the reaction condition: n_{acid}:$n_{alcohol}$:n_{cat} = 1:3.0:0.10, 130–140 °C, 3 h.

Recyclability of [HSO$_3$-pMIM]HSO$_4$

The recycling performance of [HSO$_3$-pMIM]HSO$_4$ was investigated for synthesizing a series of Nipagin esters (Table 3). [HSO$_3$-pMIM]HSO$_4$ could be reused at least five times without noticeable lowering of the catalytic activity in the esterification. In the synthesis of butyl Nipagin, after [HSO$_3$-pMIM]HSO$_4$ was reused six times, the recovery yield of FILs was 53.3%. When the quality of [HSO$_3$-PMIM]HSO$_4$ was added to the same amount used in the first time, the yield of ester resumed. It showed that the decrease of the catalytic activity of [HSO$_3$-pMIM]HSO$_4$ was mainly due to the mechanical loss; [HSO$_3$-pMIM]HSO$_4$ itself did not change. Thus it can be seen that FIL is a good catalyst for synthesizing Nipagin esters. As the length of the alcohol carbon chain increases, the melting point of the Nipagin ester decreases, and the crystallization becomes more difficult, which results in losing FILs. This indicates that the recovery yield of ILs was much lower as catalysts for synthesizing high-carbon Nipagin esters, although greater ester yield can be gained. Therefore, this question needs further exploration.

CONCLUSION

In this paper, the six acidic FILs combining the advantageous characteristics of solid acids and liquid acids were synthesized. They showed good use as dual solvent–catalysts for Nipagin esterification with good catalytic performance under mild reaction conditions. Furthermore, the synthesized FILs simply recycled and reused without noticeably decreasing the catalytic activity.

ACKNOWLEDGMENTS

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